PSJ17 Exh 99

Template Letter of Medical Necessity [BTP, Chronic Neuropathic Pain, 02-2008]

{Date}

{Medical Director's Name
Medical Director
Insurer Name
Address
City, State Zip}

Re: Denied Prescription Drug Claim for FENTORA®(fentanyl buccal tablet) [C-II] Therapy

Dear ***{Name or contact}***:

Although FENTORA is not FDA-approved for the management of breakthrough pain (BTP) in patients with chronic noncancer pain conditions, I would like to appeal this denial and provide information to support the medical necessity of using FENTORA for enrollee ***{patient name and policy number}***.

I am writing regarding a recently denied prior authorization request for FENTORA by ***{health plan name}*** for this patient due to ***{his/her}*** diagnosis of chronic neuropathic pain. FENTORA is indicated only for the management of BTP in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.[1]

With this letter, I will provide information concerning ***{patient name}***'s medical history, diagnosis and treatment(s), as well as available clinical data about the use of FENTORA in this patient population. I will describe my rationale for choosing FENTORA therapy for this patient.

Patient Information

{Healthcare Professional should populate with information regarding the patient's medical history, diagnosis, treatment(s)}

Use of Opioids in Chronic Pain

Dosing guidelines for opioid therapy for the management of chronic pain are based on extensive clinical experience in various medical conditions. Several guidelines that support the judicious use of opioids for the management of chronic pain have been published by key medical organizations, including the American Pain Society, the American Academy of Pain Medicine, the American Society of Anesthesiologists, the Federation of State Medical Boards of the United States, and the American College of Physicians.[2,3,4,5,6,7,8]

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Clinical Data

12-week Randomized, Double-blind, Placebo-controlled Study

A 12-week multicenter, open-label study with 3 within-patient, randomized, double-blind placebo-controlled treatment periods was conducted to evaluate the efficacy and safety of FENTORA in opioid-tolerant patients with BTP associated with chronic noncancer pain conditions, including neuropathic pain.[9] This was the first study to evaluate the efficacy and safety of BTP treatment over a 3-month period.

Eligible opioid tolerant adult patients experienced, on average, 1-4 BTP episodes per day which were partially controlled with rescue opioid medications. The study included an initial open-label titration phase followed by a 12-week, open-label treatment period with 3 within-patient, double-blind placebo-controlled treatment phases occurring after 4, 8, and 12 weeks of treatment. Patients entered the initial open-label dose titration phase to identify a successful dose of FENTORA defined as the single dose of 100-800 mcg providing adequate pain relief for at least 2 of 3 BTP episodes without unacceptable AEs. Patients who entered the 4-week open-label treatment period received FENTORA at their effective dose followed by a double-blind, randomized treatment for 9 consecutive BTP episodes (6 episodes were treated with FENTORA and 3 with placebo). At the completion of this phase, patients began the second open-label treatment period. The open-label/ double-blind sequence was repeated twice.

During the double-blind evaluation periods (occurring after 4, 8 and 12 weeks of treatment), pain intensity (PI, 11-point numeric scale, 0=none to 10=worst possible pain) and pain relief (PR, 5-point numeric scale, 0=no relief to 4=complete relief) scores were assessed at each time point (5, 10, 15, 30, 45, 60, 90, and 120 minutes) following treatment. The primary efficacy measure was the sum of pain intensity differences from 5 minutes though 60 minutes ($SPID_{60}$) after administration of study drug following week 12 (double-blind treatment 3). Secondary outcome measures included PID and PR at each time point during the double-blind periods (following 4, 8 and 12 weeks of treatment).

In this study, the responses to FENTORA were consistent across clinically meaningful measures after 12 weeks of treatment. The study met the primary endpoint. Improvement in pain intensity was observed as early as 15 minutes and pain relief was observed as early as 5 minutes following treatment with FENTORA compared with placebo. Adverse events were generally typical of opioids.

Randomized, Double-blind, Placebo-Controlled Study with Chronic Neuropathic Pain

A multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the efficacy and tolerability of FENTORA for breakthrough pain in patients with chronic neuropathic pain (associated with diabetic peripheral neuropathy, traumatic injury, complex regional pain syndrome, idiopathic peripheral neuropathy, and postherpetic neuralgia, resulting in functional disability of at least 3 months duration) and who were tolerant to opioid therapy.[10] These patients were on stable doses of around-the-clock (ATC) opioid medications (oral morphine ≥60 mg/day, transdermal fentanyl ≥25 mcg/hr, oxycodone ≥30 mg/day, oral

hydromorphone ≥8 mg/day or an equianalgesic dose of another opioid) for 7 days or longer prior to study enrollment) for their persistent pain.

The initial open-label dose-titration phase identified an effective dose of FENTORA (defined as the dose strength where one tablet of FENTORA provided satisfactory relief of BTP within 30 minutes for ≥2/3 episodes without unacceptable AEs). During the dose titration period, patients discontinued the study if they did not obtain satisfactory relief from BTP at any dose including the maximum dose of 800 mcg of FENTORA or if they experienced intolerable AEs. The patients who entered the double-blind phase were randomized to 1 of 3 sequences in which 9 BTP episodes were treated (6 episodes with FENTORA and 3 with placebo). Patients were allowed to use their previous standard supplemental medications to treat any BTP episodes that did not respond within 30 minutes after treatment with study medication.

Pain intensity (PI, 11-point numeric scale, 0=none to 10=worst possible pain) and pain relief (PR, 5-point numeric scale, 0=no relief to 4=complete relief) scores were assessed at baseline and at each time point (5, 10, 15, 30, 45, 60, 90, and 120 minutes) following treatment. Pain intensity differences (PID) between each time point and pre-treatment pain were calculated. The sum of pain intensity differences from 5 through 60 minutes following study drug administration ($SPID_{60}$) was the primary efficacy measure. Secondary outcome measures included PID and PR at each time point, the proportion of treated BTP episodes with ≥33% and ≥50% reduction in PI score from baseline, patients' assessment of time to meaningful PR, and the proportion of BTP episodes that required the use of usual BTP medication.

Key findings from this study showed the following:

Patient Demographics/Baseline Characteristics

- The mean age of the patients in this study was 49 years, the majority were Caucasian (92%) and 58% were female.
- Primary etiologies of persistent neuropathic pain included diabetic peripheral neuropathy (30%), complex regional pain syndrome (24%), traumatic injury (23%), idiopathic peripheral neuropathy (10%), radiculopathy (6%), postherpetic neuralgia (4%), and others (4%; "others" included multiple sclerosis, inflammatory demyelinating polyneuropathy, chronic neuropathic postoperative facial pain , and ethanol abuse).
- At baseline, the most common (≥10%) ATC opioid medications used were oxycodone/ oxycodone combination products (28%), morphine (25%), transdermal fentanyl (24%), methadone (17%), and hydrocodone-acetaminophen (9%). The median oral morphine equivalent taken as ATC dose was 160.0 mg/day (range 30 mg to 5600 mg).
- At baseline, the most common (≥10%) rescue medications used were oxycodone/ oxycodone combination products (42%), hydrocodone/ hydrocodone combination products (26%),), fentanyl/ fentanyl citrate (16%), and hydromorphone (9%). The median oral morphine equivalent taken as rescue medication for BTP was 20.0 mg/BTP episode (range 2.4 mg to 120 mg).

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Patient Disposition

- A total of 78% (80/102) of patients identified an effective dose of FENTORA between 100-800 mcg during the open-label dose-titration phase (103 patients entered this period, 102 received at least 1 dose of FENTORA and were evaluated for safety; 79 completed this phase, and 23 (22%) patients withdrew most commonly due to intolerable AEs and lack of efficacy.
    - No simple linear relationship was found between the effective dose of FENTORA and the dose of the ATC opioid taken during the study or the average dose of rescue medication used prior to the study.
- 79 patients entered the double-blind treatment phase, 77 completed the double-blind phase; 2 patients withdrew from the study due to protocol violation and noncompliance with study procedures and 75 patients were efficacy-evaluable.

Efficacy

- Mean $SPID_{60}$ scores (primary efficacy measure) were significantly higher for FENTORA than placebo (9.6 vs. 5.7, respectively, $p<0.001$).
- Mean PID and PR scores were significantly higher with FENTORA than placebo at 10 minutes ($p<0.05$, $p<0.001$, respectively) and at all subsequent time points of 15, 30, 45, 60, 90 and 120 minutes. The magnitude of treatment differences, observed in mean PID and PR scores, continued to increase through 1 hour and was maintained through 2 hours.
- Clinically significant (≥33%) improvement in PI from baseline was significantly greater with FENTORA than placebo as early as 10 minutes (9% vs 3% episodes, respectively, $p=0.008$) and at each subsequent time point at 15 ($p<0.006$), 30, 45, 60, 90 and 120 minutes ($p<0.001$). It is generally recognized that a 33% or greater reduction in pain intensity is a clinically significant improvement and is best associated with patients not needing an additional dose of rescue medication.[11,12,13]
- A clinically significant (≥50%) improvement in PI from baseline was observed with FENTORA (12% of episodes) versus placebo (5% of episodes) at 15 minutes ($P<0.001$) and at each subsequent time point ($P<0.001$).
- Patients experienced meaningful PR for more BTP episodes treated with FENTORA than for episodes in which placebo was administered (69% vs. 36%, respectively, $p<0.001$). Meaningful PR was apparent at 15 minutes and statistically significant by 30 minutes in 34% of BTP episodes treated with FENTORA vs. 15% for placebo ($p<0.001$).
- Rescue medication was used for 77 (36%) of 213 BTP episodes for which placebo was used compared to 59 (14%) of 432 BTP episodes for those receiving FENTORA. These data resulted in a relative risk ratio of 0.28, with 95% confidence interval (CI) 0.18-0.42. Therefore, patients receiving placebo were approximately 3.5 times more likely to use supplemental opioids for BTP episodes than those receiving FENTORA.

Safety Profile

- In this study, FENTORA was generally well tolerated at doses of 100-800 mcg. Overall, AEs were reported by 63% (64/102) of patients.

- The most frequently occurring AEs (≥5%) were nausea (13%), dizziness (13%), somnolence (10%) and vomiting (5%); all of which are typical of opioid side effects. These AEs were more frequent during the dose-titration phase than during the double-blind treatment period (54% vs. 28%, respectively).
- A total of twelve (12%) patients discontinued the study due to AEs, most commonly nausea, vomiting, somnolence and confusion, all of which occurred during the dose-titration period.
- Mild application site AEs (pain, irritation, ulcer, and anesthesia) were reported in 8 (8%) of patients, all of which resolved without residual effect. None of the 8 patients discontinued the study due to application site reactions.
- There were no reports of respiratory depression.
- One patient experienced a serious AE (angina pectoris) during the double-blind period which was considered not related to the study drug by the investigator.

In summary, in the clinical trial of FENTORA for chronic neuropathic pain, approximately 80% of patients found an effective dose of FENTORA in the range of 100 mcg to 800 mcg. FENTORA was found to be efficacious compared to placebo, producing significant reduction in pain intensity and significant greater pain relief, both as early as 10 minutes after tablet administration and at all subsequent time points through 120 minutes, the last time point measured. Treatment with FENTORA was generally well tolerated and AEs were typical of opioid side effects.

Open-label Study

An 18-month, open-label study was conducted to evaluate the long-term safety and tolerability of FENTORA in opioid-tolerant patients with BTP and chronic noncancer pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, complex regional pain syndrome, chronic low back pain, traumatic injury, osteoarthritis or chronic headache.

Eligible patients experienced 1-4 BTP episodes per day and were managed with ATC opioid medications (oral morphine ≥60 mg/day, or an equianalgesic dose of another opioid as ATC therapy, or transdermal fentanyl ≥50 mcg/hr, for 7 days or longer prior to enrollment into the study) for their persistent pain. This study was open to new patients (those naïve to FENTORA) and to patients who had completed 1 of 2 randomized double-blind FENTORA efficacy studies. For new patients, the study consisted of a screening visit, a dose-titration period and an 18-month open-label maintenance period. The effective dose for treatment naïve patients (100-800 mcg) was determined during the dose-titration period and was defined as the single dose strength of FENTORA that provided adequate analgesia (sufficient pain relief within 30 minutes), for each of approximately 2 of 3 BTP episodes, without unacceptable AEs for the majority of BTP episodes. For patients who had previously participated in either of the two short-term double-blind studies discussed above, the study consisted of only an 18-month maintenance treatment period at their previously identified effective dose.

Safety Profile

Interim safety data was published for 94 patients.[14]

- FENTORA was generally well tolerated in the dose range of 100 mcg to 800 mcg with a relatively low incidence of AEs (23%).
- The most common AEs that occurred in the 94 patients were nausea (7%), dizziness (5%), back pain (4%), headache (4%), dyspepsia (3%), application site pain (2%), arthralgia (2%), and anxiety (2%).
- Four patients reported oral mucosal AEs (pain, irritation, ulceration, or vesicles) associated with tablet application site which resolved within 1-15 days for 3 patients. The resolution time for the fourth patient was unknown.
- There were no reports of respiratory depression or death.

In summary, based on the interim analysis of a long-term safety study, FENTORA was well tolerated at doses ranging from 100 to 800 mcg for the management of BTP in opioid-tolerant patients with chronic noncancer pain.

FENTORA Product Summary[1]

FENTORA is indicated only for the management of breakthrough pain (BTP) in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

In a pivotal trial of FENTORA, onset of efficacy was demonstrated within 15 minutes in some opioid tolerant cancer patients, with duration of efficacy demonstrated up to 60 minutes (last time point measured).

Important Safety Information

- Postmarketing reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. These deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing.

- Use FENTORA only for labeled indications

- FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

- FENTORA is contraindicated in the management of acute pain, postoperative pain, headache or migraine.

- FENTORA is not a generic version of Actiq (oral transmucosal fentanyl citrate). When prescribing, do not convert patients from Actiq to FENTORA on a mcg per mcg basis. When

dispensing, do not substitute FENTORA for other fentanyl products as this may result in fatal overdose.

- Follow dosing instructions carefully:
  - For opioid tolerant patients not being converted from Actiq, the initial dose of FENTORA is always 100 mg.
  - For patients being converted from Actiq, please consult the Initial Dosing Recommendations table in the enclosed prescribing information for FENTORA.
  - Patients should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.
  - Patients should NOT take more than 2 doses of FENTORA per BTP episode (separated by at least 30 minutes using the same dosage strength)
  - Patients MUST wait at least 4 hours before treating another BTP episode with FENTORA
- FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.
- Patients and caregivers must be instructed that FENTORA contains a medicine in an amount that can be fatal to a child and thus, should keep all tablets out of the reach of children, and properly discard of any unused tablets as soon as they are no longer needed.
- Use with strong or moderate cytochrome P450 3A4 (CYP3A4) inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

In FENTORA cancer clinical trials, FENTORA was generally well tolerated at doses of 100 mcg to 800 mcg. The most frequently occurring adverse events (≥10% of patients in either titration or post-titration) were nausea, vomiting, fatigue, dizziness, anemia, constipation, peripheral edema, dehydration, asthenia and headache. No corrections were made for concomitant use of around-the-clock opioids or cancer-related symptoms. In addition, application site reactions, which occurred in 10% of patients in all FENTORA studies, tended to occur early in treatment, were self-limited, and resulted in treatment discontinuation in 2% of patients.

Rationale for Therapy
{Healthcare Professional should populate with his/her own clinical judgment for use of this therapy in his/her patient.}

Thank you for your consideration. Please contact me at ***{physician telephone number}*** if you require additional information.

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Sincerely,
{Physician Name
Title}

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[1] FENTORA® (fentanyl buccal tablet) [Current approved prescribing information]. Frazer, PA: Cephalon, Inc.

[2] Public Policy Statement on the Rights and Responsibilities of Healthcare Professionals in the use of Opioids for the Treatment of Pain. 2004. Available at: http://www.ampainsoc.org/advocacy/rights.htm. Accessed 18 October 2007.

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[9] Farrar, JT, Michna, E, and Messina, J et al.: Fentanyl buccal tablet (FBT) in opioid-tolerant patients with non-cancer-related breakthrough pain on around-the-clock opioids: A 12-week study using a novel double-blind, placebo-controlled design. [Abstract] *Pain Medicine*. 9(1): 102, 2008.

[10] Simpson DM, Messina J, Xie F, et al. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: A multicenter, randomized, double-blind, placebo-controlled study. *Clinical Therapeutics*. 29(4):588-601, 2007.

[11] Farar JT, Portenoy R, Berlin JA, et al. Defining the clinically important pain outcome measures. *Pain* 88:287-294, 2000.

[12] Farrar JT, Young JP, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 94:149-158, 2001.

[13] Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 113:9-19, 2005.

[14] Hale M, Webster L, Peppin J, et al. Open-label study of fentanyl effervescent buccal tablets in patients with chronic pain and breakthrough pain: Interim safety and tolerability results. [Poster presentation]. Presented at the American Academy of Pain Medicine's Annual Meeting, San Diego, CA, February 22-25, 2006.